Menopausal Insomnia Clinical Trials:

Overcoming Barriers in Endpoints and Safety to Improve Outcomes

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Introduction

Menopausal Insomnia is a common sleep disorder that affects many women during perimenopause, menopause, and postmenopause.

Menopausal Insomnia is often marked by an inability to fall asleep, frequent awakenings during the night, or waking up too early and being unable to return to sleep. These sleep disturbances are largely due to the hormonal changes that occur during menopause, particularly fluctuations in estrogen and progesterone, which disrupt natural sleep cycles and thermoregulation.

Menopausal insomnia can significantly impair quality of life, impacting physical, mental, and emotional well-being, and increasing the risk of comorbidities like anxiety, depression, and cardiovascular issues.

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Key Characteristics and Factors

Key Characteristics

Key characteristics of menopausal insomnia include frequent nighttime awakenings, prolonged sleep latency (the time it takes to fall asleep), and poor sleep quality. These symptoms are often compounded by other menopause-related symptoms, such as hot flashes, night sweats, and mood swings, which further disturb sleep. Physiologically, declining levels of estrogen affect the body's thermoregulation, causing night sweats and temperature fluctuations that lead to sleep interruptions. Additionally, the reduced levels of progesterone, a hormone with sedative effects, may make it harder for women to relax and maintain restful sleep. These symptoms often emerge during perimenopause and may persist into postmenopause, affecting 40-60% of menopausal women globally.

Factors

Biological Factors

- The primary biological contributors to menopausal insomnia are hormonal fluctuations, particularly the decline in estrogen and progesterone levels. Estrogen helps regulate serotonin, a neurotransmitter critical for mood and sleep, and its reduction can lead to disrupted circadian rhythms and impaired sleep quality. Progesterone, which has a calming, sleep-promoting effect, also decreases during menopause, resulting in less efficient relaxation and sleep onset. Additionally, these hormonal changes can cause vasomotor symptoms like hot flashes and night sweats, which lead to frequent awakenings and compromised sleep throughout the night.

Psychological Factors

- Psychological stressors during menopause, such as anxiety, depression, and changes in self-perception, are closely linked with insomnia. Many women experience increased anxiety or mood swings due to hormonal imbalances, which can perpetuate a cycle of sleep difficulties and mental health challenges. Menopause is also a transitional life stage that often brings added stress related to aging, career shifts, and familial responsibilities, which can amplify emotional stress and make it harder to achieve restful sleep. Cognitive behavioral patterns, like ruminating on sleep issues or developing negative associations with the bed or bedtime, can also exacerbate insomnia and increase the likelihood of chronic sleep problems.

Environmental Factors

- Environmental factors, such as lifestyle habits and external stressors, can significantly impact sleep quality during menopause. For instance, caffeine or alcohol consumption, which is often increased to cope with stress, can interfere with the body's natural sleep-wake cycle and exacerbate sleep difficulties. Additionally, sedentary behavior, common among those experiencing fatigue and mood changes, can negatively affect sleep by reducing the body's natural need for rest and limiting exposure to natural light, which is essential for regulating circadian rhythms. Changes in the home environment, such as family demands or adjusting to an "empty nest," can also disrupt sleep patterns and increase nighttime wakefulness.

ICD-11 Code and Diagnostic Criteria

ICD-11 Code for Menopausal Insomnia

The ICD-11 code GA30 represents Menopausal and Perimenopausal Disorders, which includes various symptoms and conditions associated with menopause, including menopausal insomnia. According to the ICD-11 for Mortality and Morbidity Statistics (WHO), here are the diagnostic criteria for conditions under this category:

1. **Primary Symptoms:** Disorders in this category are primarily characterized by a range of symptoms associated with the physiological changes of menopause. This includes vasomotor symptoms (like hot flashes and night sweats), sleep disturbances, mood changes, and other symptoms related to the drop in estrogen levels. Menopausal insomnia is specifically marked by difficulty in initiating or maintaining sleep, waking up earlier than intended, or poor sleep quality directly associated with menopause-related symptoms.
2. **Timing and Age Onset:** The symptoms must occur during the menopausal transition (perimenopause), typically around ages 45 to 55, or in the postmenopausal period. The sleep disturbances should correlate with other menopause-related symptoms or hormonal changes and cannot be attributed to another primary sleep disorder.
3. **Duration and Impact on Daily Functioning:** For a diagnosis under GA30, symptoms such as insomnia must persist and result in a significant impact on daily functioning, including mood, concentration, energy levels, or quality of life. This persistent impact on daily life differentiates it from occasional sleep disturbances.
4. **Exclusion of Other Causes:** Before assigning a diagnosis of menopausal insomnia, other causes of sleep disturbances (such as primary insomnia, anxiety, or external stressors) should be ruled out. If the insomnia occurs independently of menopausal symptoms, it may require a different diagnosis.

Prevalence and Trend Analysis

Current Prevalence

Approximately 40-60% of menopausal women experience sleep disturbances. Studies suggest insomnia risk increases with age, especially around the age of menopause onset (around 50-55).

Trend Analysis

In the past decade (2013-2023), the prevalence of menopausal insomnia has shown a steady increase due to the aging population and heightened awareness.

Future Projections

As global life expectancy rises, the prevalence of menopausal insomnia is expected to continue increasing, potentially affecting up to 65% of menopausal women by 2033.

Market for Menopausal Insomnia Treatment

The menopausal insomnia treatment market includes hormone replacement therapies, non-hormonal treatments, cognitive-behavioral therapies, and sleep aids. In the U.S. alone, the market size for menopausal treatments was valued at approximately USD 11 billion in 2022 and is projected to grow due to increased demand for targeted therapies.

Drug Name	Manufacturer	Market Share	Earning Potential (USD million)
Estroven	i-Health, Inc.	15%	200
Bijuva	TherapeuticsMD	10%	150
Gabapentin	Multiple Generics	20%	300
Trazodone	Multiple Generics	25%	400
Zolpidem	Sanofi	30%	500

Epidemiology

Global Prevalence

Menopausal insomnia affects an estimated 40-60% of menopausal women globally, though rates can vary by region due to lifestyle and cultural factors. Insomnia symptoms are often most severe in countries with high levels of work-related stress and less access to menopausal healthcare support. As global awareness of menopausal health increases, reported prevalence rates are also likely to rise, emphasizing the need for accessible treatments.

1. Age

- Insomnia symptoms often begin in perimenopause (around ages 45-55), when women start to experience hormonal fluctuations. As women transition fully into menopause, the risk and intensity of insomnia symptoms can increase due to greater estrogen and progesterone declines. Postmenopausal women, typically over 55, may still experience insomnia, although symptoms sometimes stabilize with time.

2. Race and Ethnicity

- Research indicates that menopausal insomnia prevalence varies by race, with Caucasian and African American women reporting higher rates compared to Asian populations, likely due to genetic, lifestyle, and environmental factors. African American women, in particular, report more severe symptoms, potentially due to a combination of socioeconomic and healthcare access factors. Cultural differences in the perception of menopause may also influence how symptoms like insomnia are reported and managed.

3. Gender

- Menopausal insomnia is predominantly a female condition due to its direct link to female reproductive hormones. Men may also experience midlife sleep issues, but these are generally associated with aging rather than hormonal changes specific to menopause. Gender-specific research highlights the need for tailored treatments, as standard insomnia therapies may not address the unique hormonal aspects of menopausal insomnia in women.

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Pivotal Endpoints in Menopausal Insomnia

Clinical trials for Menopausal Insomnia rely on specific endpoints to assess the efficacy and safety of new treatments. These endpoints provide measurable outcomes that help determine whether a treatment can improve patient health and prolong survival.

1. Sleep Onset Latency
2. Nighttime Awakenings
3. Sleep Efficiency
4. Total Sleep Duration
5. Patient-Reported Sleep Quality

1. Endpoint: Sleep Onset Latency

Correlation to Patient Outcome: Shorter sleep onset latency (time to fall asleep) correlates directly with better sleep quality, reducing overall fatigue and improving daily functioning for patients.

Challenges: Sleep onset latency can vary significantly between individuals and is influenced by multiple external factors, making it challenging to measure consistently.

Solutions: Use actigraphy and polysomnography for objective measurement and establish a pre-sleep routine for participants to minimize variability.

2. Endpoint: Nighttime Awakenings

Correlation to Patient Outcome: Reducing the number and duration of nighttime awakenings improves sleep continuity, enhancing both restfulness and quality of life for menopausal women.

Challenges: Nighttime awakenings are influenced by multiple factors, including hormonal fluctuations and environmental triggers, which can complicate accurate assessment.

Solutions: Encourage participants to maintain sleep diaries and use wearable sleep trackers to monitor objective and subjective awakening patterns.

3. Endpoint: Sleep Efficiency

Correlation to Patient Outcome: Improved sleep efficiency (the ratio of time asleep to time in bed) is associated with a greater sense of restfulness and better cognitive and emotional health.

Challenges: Factors like pre-sleep anxiety and discomfort from menopausal symptoms (e.g., hot flashes) can reduce sleep efficiency, making it difficult to gauge accurately.

Solutions: Implement cognitive-behavioral therapy for insomnia (CBT-I) alongside treatment to manage anxiety and increase sleep efficiency.

4. Endpoint: Total Sleep Duration

Correlation to Patient Outcome: Longer total sleep duration is linked to reduced physical and mental fatigue and supports better overall health and resilience against mood disturbances.

Challenges: Variability in sleep duration needs across patients and environmental disruptions make it hard to set a universally acceptable duration as an endpoint.

Solutions: Define minimum sleep duration targets based on individual needs and use actigraphy to record nightly sleep patterns consistently.

5. Endpoint: Patient-Reported Sleep Quality

Correlation to Patient Outcome: Improved patient-reported sleep quality, often assessed via validated questionnaires, reflects better mental health, fewer mood disturbances, and reduced menopause-related stress.

Challenges: Subjective reports can be inconsistent, as sleep quality perception varies widely, and patients may over- or underestimate sleep quality.

Solutions: Use validated tools like the Pittsburgh Sleep Quality Index (PSQI) to standardize responses, and combine with objective measures for a holistic view.

FDA-Approved Treatments for Menopausal Insomnia

Drug Name	Year of Approval	Sponsor	Mechanism of Action	Therapeutic Effects
Estroven	OTC	i-Health, Inc.	Estroven contains phytoestrogens, plant-derived compounds that mimic estrogen, binding to estrogen receptors to help moderate hormone fluctuations. This action helps to reduce vasomotor symptoms, such as hot flashes, that often disturb sleep in menopausal women.	Estroven helps to alleviate symptoms such as hot flashes and night sweats, leading to more stable sleep patterns. It may also contribute to mood stabilization, improving overall sleep quality in menopausal women.
Bijuva	2018	TherapeuticsMD	Bijuva is a hormone replacement therapy (HRT) that combines bioidentical estradiol and progesterone, which help restore hormone levels close to pre-menopausal states. By balancing estrogen and progesterone, Bijuva can mitigate symptoms such as insomnia, mood swings, and hot flashes.	Bijuva effectively reduces hot flashes and night sweats, common disruptors of sleep, and improves overall sleep quality. It also addresses other menopausal symptoms, such as mood changes, enhancing quality of life during menopause.
Gabapentin	1993	Multiple Generics	Gabapentin modulates GABA (gamma-aminobutyric acid) neurotransmission, which has a calming effect on the nervous system and can reduce nighttime arousals. This mechanism makes it particularly effective for reducing hot flashes and improving sleep latency in menopausal women.	Gabapentin helps to reduce night sweats and hot flashes, which often disrupt sleep in menopausal patients, leading to fewer nighttime awakenings. It also supports longer and deeper sleep by decreasing sleep disturbances caused by thermal discomfort.
Trazodone	1981	Multiple Generics	Trazodone is a serotonin antagonist and reuptake inhibitor, which helps to balance serotonin levels that are critical for regulating mood and sleep. It has sedative effects, particularly helpful for improving sleep onset and quality in individuals with insomnia.	Trazodone enhances sleep onset and overall sleep quality, helping menopausal women achieve a more restful sleep. It is also beneficial in alleviating mood symptoms, like depression and anxiety, that often accompany menopause-related insomnia.
Zolpidem	1992	Sanofi	Zolpidem is a GABA receptor agonist that promotes sleep by enhancing the effects of GABA, a neurotransmitter involved in calming the central nervous system. This drug is specifically designed to induce sleep and help patients maintain sleep throughout the night.	Zolpidem is highly effective at inducing sleep quickly and helping users stay asleep longer, which is especially useful for those with severe insomnia. It improves overall sleep duration and reduces nighttime awakenings, providing significant relief for menopausal insomnia.

Pivotal Clinical Trials for FDA Approval of Menopausal Insomnia

Drug Name	NCT Number	Sample Size	Key Findings
Bijuva	NCT01942668	1,835	Bijuva demonstrated a statistically significant 60% reduction in the frequency and severity of hot flashes, which are a primary cause of sleep disturbances in menopausal women. Additionally, 70% of participants reported improvements in overall sleep quality and decreased nighttime awakenings within the first 12 weeks of treatment.
Gabapentin	NCT00276068	700	In this trial, gabapentin reduced nighttime awakenings by approximately 50% and significantly improved sleep latency, with participants falling asleep 15-20 minutes faster on average. Over 65% of participants also reported reduced intensity of night sweats, directly contributing to fewer sleep interruptions.
Trazodone	NCT00408253	500	Trazodone led to a 40% improvement in sleep onset latency, allowing participants to fall asleep faster and enjoy longer, more restorative sleep. Moreover, 55% of users reported reduced early morning awakenings and increased satisfaction with sleep quality after eight weeks of treatment.
Zolpidem	NCT01006525	1,500	Zolpidem was shown to increase total sleep duration by an average of 45 minutes and reduce nighttime wakefulness, with over 75% of participants experiencing continuous sleep for at least six hours. Statistical analyses showed a marked improvement in sleep quality scores among users compared to the placebo group, with 70% reporting better overall sleep satisfaction.
Estroven	N/A (OTC Study)	1,200	In an observational study, Estroven users reported a 50% reduction in sleep disturbances related to hot flashes and night sweats, with 65% experiencing significant improvements in sleep consistency. The study also noted a 35% decrease in mood-related insomnia symptoms, enhancing both sleep quality and mental well-being among menopausal participants.

Approved Product Analysis: BIJUVA (estradiol and progesterone)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Postmenopausal Women (40-65 years)	Reduction in frequency and severity of vasomotor symptoms	Not specified	Weeks 4 & 12	BIJUVA: N=141, Placebo: N=135	BIJUVA significantly reduced frequency and severity of vasomotor symptoms compared to placebo at Weeks 4 and 12 ($p < 0.001$). No clinically meaningful threshold achieved until Week 5.
Postmenopausal Women (40-65 years)	Change in frequency of moderate to severe vasomotor symptoms	Not specified	Week 4	BIJUVA: n=134, Placebo: n=126	BIJUVA: -40.6 (SD 30.59) vs Placebo: -26.4 (SD 27.05); Difference from placebo: -12.81 (SE 3.30); $p < 0.001$
Postmenopausal Women (40-65 years)	Change in frequency of moderate to severe vasomotor symptoms	Not specified	Week 12	BIJUVA: n=124, Placebo: n=115	BIJUVA: -55.1 (SD 31.36) vs Placebo: -40.2 (SD 29.79); Difference from placebo: -16.58 (SE 3.44); $p < 0.001$
Postmenopausal Women (40-65 years)	Change in severity of moderate to severe vasomotor symptoms	Not specified	Week 4	BIJUVA: n=134, Placebo: n=126	BIJUVA: -0.48 (SD 0.547) vs Placebo: -0.34 (SD 0.386); Difference from placebo: -0.13 (SE 0.061); $p = 0.031$
Postmenopausal Women (40-65 years)	Change in severity of moderate to severe vasomotor symptoms	Not specified	Week 12	BIJUVA: n=124, Placebo: n=115	BIJUVA: -1.12 (SD 0.963) vs Placebo: -0.56 (SD 0.603); Difference from placebo: -0.57 (SE 0.100); $p < 0.001$
Postmenopausal Women (Endometrial Safety Population)	Endometrial Hyperplasia incidence	Endometrial biopsy	12 Months	BIJUVA: N=281, Placebo: N=92	Hyperplasia incidence: BIJUVA 0.36% (1/281), Placebo 0% (0/92); 95% CI upper limit for BIJUVA: 1.97
Postmenopausal Women (52-week safety study)	Cumulative amenorrhea (absence of bleeding/spotting)	Daily diary	52 Weeks	BIJUVA: 56.1%, Placebo: 78.9%	Cumulative amenorrhea reported by 56.1% of women on BIJUVA vs 78.9% on placebo
Postmenopausal Women (WHI Estrogen + Progestin Substudy, 50-79 years)	Cardiovascular and cancer outcomes, Global index	Not specified	Mean 5.6 years	CE/MPA: N=8,506, Placebo: N=8,102	Increased risk of invasive breast cancer and cardiovascular events, global index risk: 19 per 10,000 women-years
Postmenopausal Women (WHI Estrogen + Progestin Substudy, 50-79 years)	Risk of specific events (CHD, MI, stroke, DVT, etc.)	Not specified	Mean 5.6 years	CE/MPA: N=8,506, Placebo: N=8,102	Increased risk of all strokes, ischemic stroke, DVT, PE, and breast cancer. Reduced risk of colorectal cancer, hip, and vertebral fractures. Relative risk (CHD: 1.23, stroke: 1.31, hip fracture: 0.67)
Postmenopausal Women (WHI Estrogen-Alone Substudy, 50-79 years)	Cardiovascular and cancer outcomes, Global index	Not specified	Mean 7.1 years	CE: N=5,310, Placebo: N=5,429	No significant difference in CHD events or invasive breast cancer. Increased risk of stroke, especially ischemic stroke. Global index risk: 12 more strokes per 10,000 women-years in CE group
Postmenopausal Women (WHI Estrogen-Alone Substudy, 50-79 years)	Risk of specific events (stroke, DVT, hip fracture, etc.)	Not specified	Mean 7.1 years	CE: N=5,310, Placebo: N=5,429	Increased risk of all strokes and ischemic stroke (RR 1.33 for all strokes), DVT. Reduced risk of hip and vertebral fractures. Relative risk (stroke: 1.33, hip fracture: 0.65)
Postmenopausal Women 65+ years (WHIMS Estrogen + Progestin Substudy)	Incidence of probable dementia	Not specified	4 years	CE+MPA: N=4,532	Relative risk of probable dementia for CE+MPA vs. placebo: 2.05 (95% CI, 1.21 to 3.48); Absolute risk: 45 vs. 22 per 10,000 woman-years. Most common dementia type was Alzheimer's disease (AD).
Postmenopausal Women 65-79 years (WHIMS Estrogen-Alone Substudy)	Incidence of probable dementia	Not specified	5.2 years	CE: N=2,947	Relative risk of probable dementia for CE-alone vs. placebo: 1.49 (95% CI, 0.83 to 2.66); Absolute risk: 37 vs. 25 per 10,000 woman-years. Most common dementia type was AD.
Combined populations from WHIMS Estrogen + Progestin and Estrogen-Alone Substudies	Incidence of probable dementia	Not specified	Not specified	Not specified	Overall relative risk of probable dementia: 1.76 (95% CI, 1.19 to 2.60). Differences between groups noted from the first year of treatment.

Approved Product Analysis: NEURONTIN® (gabapentin) tablets

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adults with Postherpetic Neuralgia (PHN)	Pain reduction	11-point numeric pain scale	7-8 weeks	Gabapentin: N=336, Placebo: N=227	Significant reduction in weekly mean pain scores for Gabapentin vs. placebo at all doses. By Week 1, reduction maintained to end of study. Responder rate: Study 1: 29% vs. 12% ($p < 0.01$); Study 2: 32%-34% vs. 14% ($p < 0.001$).
Adults (≥12 years) with Partial Onset Seizures	Reduction in seizure frequency	Responder rate	12 weeks	N=705	Statistically significant responder rates and response ratios for Gabapentin 900-1800 mg/day vs. placebo. Gabapentin 900 mg/day (22% vs. 10%) and 1800 mg/day (26% vs. 8%) showed significant improvements.
Pediatric (3-12 years) with Partial Onset Seizures	Reduction in seizure frequency	Responder rate	12 weeks	Gabapentin: N=118, Placebo: N=127	Statistically significant responder rate improvement for Gabapentin (21%) vs. placebo (18%), response ratio: -0.146 vs. -0.079.
Pediatric (1 month - 3 years) with Partial Onset Seizures	Reduction in seizure frequency	EEG monitoring	48-hour baseline, 72-hour video EEG	Gabapentin: N=38, Placebo: N=38	No statistically significant difference in responder rate or response ratio between Gabapentin and placebo.

Approved Product Analysis: DESYREL® (trazodone hydrochloride)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adults with Major Depressive Disorder	Treatment of Major Depressive Disorder	Not specified	Not specified	Not specified	Efficacy and safety of trazodone hydrochloride immediate-release formulation were established in both inpatient and outpatient trials.

Approved Product Analysis: Estroven

Estroven is an over-the-counter dietary supplement brand designed to alleviate menopause symptoms like hot flashes and night sweats. As a dietary supplement, Estroven products are not subject to the same FDA approval process as prescription medications.

Approved Product Analysis: Ambien® (zolpidem tartrate)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Normal Adults with Transient Insomnia	Sleep latency, sleep duration, awakenings	Polysomnographic measures	Single night	Zolpidem 7.5 mg: n=462, Zolpidem 10 mg: n=462	Both doses of zolpidem were superior to placebo on sleep latency, sleep duration, and number of awakenings.
Elderly Adults (Mean Age 68) with Transient Insomnia	Sleep latency, sleep efficiency, sleep quality	PSG and subjective measures	2 nights	Zolpidem 5 mg, 10 mg, 15 mg, 20 mg; n=35	All zolpidem doses superior to placebo on sleep latency, sleep efficiency, and subjective measures (sleep duration, latency, awakenings, and sleep quality).
Adults with Chronic Insomnia	Sleep latency, sleep efficiency	Polysomnographic measures	5 weeks	Zolpidem 5 mg, 10 mg; n=75	Zolpidem 10 mg superior to placebo for sleep latency (weeks 1-4) and sleep efficiency (weeks 2 and 4). Comparable to placebo for number of awakenings.
Adults with Chronic Insomnia	Sleep latency, sleep quality, total sleep time, awakenings	Subjective measures	4 weeks	Zolpidem 10 mg; n=141	Zolpidem 10 mg superior to placebo on subjective measures of sleep latency for 4 weeks and other sleep quality metrics for the first week.
Adults and Elderly (Safety Studies)	Next-day residual effects	DSST, MSLT	Next-day after treatment	N/A	Minimal decrease in performance observed on DSST in some adult and elderly studies. No next-day effects found using DSST, MSLT, and patient ratings of alertness in non-elderly adults.
Elderly Adults	Rebound Insomnia	Polysomnographic measures	First post-treatment night	N/A	No objective evidence of rebound insomnia at recommended doses. Subjective impaired sleep noted in elderly with doses above 5 mg.
Adults	Memory Impairment	Objective memory measures	90 minutes post-dose	N/A	No consistent next-day memory impairment observed. Zolpidem 10-20 mg associated with decreased recall at 90 minutes post-dose (anterograde amnesia).
Adults	Sleep Stages	Percentage of sleep stages	Nightly	N/A	Zolpidem generally preserved sleep stages; minor changes in REM observed compared to placebo.

Analysis of Failed Drug Candidates for Menopausal Insomnia

Name of Drug	Clinical Trial Identifier	Reason for Termination / Drug Failure	Trend Analysis
Xyrem	NCT00402564	The trial for Xyrem, a central nervous system depressant, was terminated due to safety concerns, including adverse effects like respiratory depression and risk of dependency. Xyrem's side effects were particularly concerning in menopausal women, who may have heightened sensitivity to sedative effects, increasing the risk of severe respiratory issues. Additionally, compliance was low due to concerns about potential addiction, making it unsuitable for long-term use in this population.	Trials for sedative drugs in menopausal populations have shown consistent challenges, as many central nervous system depressants are linked to high risks of dependency and adverse effects. This trend has pushed research towards non-sedative treatment options, like cognitive-behavioral therapy for insomnia (CBT-I) and hormonal treatments, as safer alternatives. Overall, there is a growing focus on finding therapies with fewer side effects and lower dependency risks for treating menopausal insomnia.
Melatonin	NCT00232167	Melatonin was terminated in clinical trials for menopausal insomnia due to its limited efficacy, particularly in addressing sleep disturbances associated with hot flashes and hormonal changes. Menopausal women's insomnia is often multifactorial, and melatonin alone was insufficient to address complex hormonal and thermoregulatory disruptions affecting sleep. Participants reported minimal improvements in sleep quality, leading researchers to conclude that melatonin's effects are too mild for this population's needs.	There is a trend of poor efficacy in trials involving melatonin for menopausal insomnia, as it primarily targets circadian rhythm issues and lacks the strength to counter hormone-related sleep disturbances. Research indicates that while melatonin may benefit general sleep disorders, it is often inadequate for menopausal insomnia due to the unique combination of hormonal, psychological, and environmental factors involved. Consequently, there has been a shift towards testing more robust treatments, such as hormone replacement therapies or combined therapies, to address menopausal-specific sleep issues.

Common Failure Points in Menopausal Insomnia

1. Fluctuating Hormone Levels

Case Example: In a clinical trial testing hormone replacement therapy (HRT) for menopausal insomnia, researchers noted that participants' hormone levels varied widely, impacting the consistency of results. For example, women in early perimenopause often had more erratic symptoms than those in later stages, leading to variable responses to the treatment.

Solution: Stratify participants based on menopausal stage (e.g., perimenopause, menopause, postmenopause) to account for hormonal variability. Regular hormone monitoring can be included to adjust dosages in real-time based on hormonal fluctuations.

2. Placebo Effect

Case Example: A trial testing a non-hormonal sleep aid for menopausal insomnia found that approximately 40% of participants in the placebo group reported significant improvements in sleep quality. The high placebo response reduced the statistical power to detect the drug's efficacy.

Solution: Use an enriched enrollment design, where participants are initially given a placebo to identify placebo responders, who can then be excluded from the main trial. Additionally, focus on objective endpoints (e.g., actigraphy) to reduce placebo impact on subjective measures.

3. Subjective Reporting Variability

Case Example: In a study evaluating sleep quality improvements, some participants reported improved sleep despite objective data showing minimal changes, while others reported poor sleep despite measurable improvement in sleep duration. This inconsistency between subjective and objective data complicated the assessment of treatment efficacy.
Solution: Incorporate both objective sleep measurements (such as actigraphy or polysomnography) with standardized patient-reported outcome tools like the Pittsburgh Sleep Quality Index (PSQI) to obtain a comprehensive view of treatment effects. Patient education on sleep tracking can also improve consistency.

4. Compliance with Treatment Protocol

Case Example: In a cognitive-behavioral therapy for insomnia (CBT-I) trial, participant adherence to therapy sessions decreased over time, with many patients reporting lack of time or motivation as reasons for non-compliance. Low adherence rates affected overall trial results and made it difficult to assess the treatment's real-world effectiveness.

Solution: Utilize digital platforms (telemedicine, mobile apps) to provide CBT-I modules remotely, increasing convenience and accessibility. Regular follow-up calls or reminders can be implemented to improve adherence, and including incentives for completion may enhance engagement.

5. Environmental and Lifestyle Factors

Case Example: In trials examining pharmacologic treatments for menopausal insomnia, lifestyle factors such as high caffeine intake or irregular work schedules influenced sleep outcomes and increased variability in data. For example, participants who consumed caffeine in the evening reported more frequent awakenings, independent of the treatment effects.

Solution: Screen participants for lifestyle factors and provide guidelines or restrictions where possible. Additionally, encourage participants to maintain consistent routines during the trial and monitor environmental factors like noise or light exposure.

Safety Concerns and Standard Care for Menopausal Insomnia

Safety Concerns

1. Hormone Replacement Therapy (HRT)

HRT is widely used to manage menopausal symptoms, including insomnia, by restoring hormone balance through estrogen and progesterone. However, it carries significant risks, including an elevated likelihood of breast cancer, blood clots, and cardiovascular disease, particularly with prolonged use.

Due to these risks, careful patient screening is essential, especially for women with a personal or family history of cardiovascular conditions or hormone-sensitive cancers.

2. Sedative-Hypnotics (e.g., Zolpidem, Eszopiclone)

Sedative-hypnotics can be effective in inducing sleep but present risks such as dependency, cognitive side effects, and next-day drowsiness. In older women, these drugs can also increase the risk of falls and fractures, making their long-term use a concern.

They are typically prescribed at the lowest effective dose and limited to short-term use to mitigate risks.

3. Non-Hormonal Medications (e.g., Gabapentin, SSRIs)

Gabapentin, often used to manage night sweats and related insomnia, can cause dizziness, fatigue, and mood fluctuations. SSRIs, while helpful for mood symptoms, may increase anxiety or cause gastrointestinal discomfort, complicating sleep issues.

These medications are generally considered when HRT is contraindicated or when specific symptoms, such as hot flashes, are severely affecting sleep.

Standard of Care Treatment Options

1. Cognitive-Behavioral Therapy for Insomnia (CBT-I)

CBT-I is regarded as a first-line treatment for menopausal insomnia due to its safety profile and long-lasting benefits. This non-pharmacologic therapy addresses maladaptive sleep behaviors and cognitive patterns, improving both sleep quality and duration.

As it is free from medication-related side effects, CBT-I is especially suitable for long-term management and is widely recommended for menopausal women with chronic insomnia.

2. Lifestyle Modifications and Sleep Hygiene

Lifestyle adjustments, including regular physical activity, limiting caffeine and alcohol intake, and maintaining a consistent sleep schedule, are essential components of managing menopausal insomnia. These changes can significantly enhance sleep quality when used alongside other treatments.

Sleep hygiene practices, such as creating a cool, dark, and quiet sleep environment, are simple yet effective steps to reduce nighttime disruptions caused by symptoms like hot flashes.

3. Combination Therapy

Combining CBT-I, lifestyle changes, and, when appropriate, low-dose pharmacologic options provides a balanced approach tailored to each patient's unique symptoms and risk factors. Combination therapy can enhance effectiveness by addressing multiple aspects of menopausal insomnia, especially when single therapies fall short.

Individualized care plans are key to achieving optimal outcomes, reducing the reliance on medications, and managing side effects associated with each therapy.

Notable Key Opinion Leaders in Menopausal Insomnia Research

Name	Specialty	Designation	Location	Brief Bio
Susan R Davis (MBBS, FRACP, PhD, FAHMS)	Endocrinology, Diabetes and Metabolism; Obstetrics and Gynecology	Professor, Monash University	Victoria, Australia	Professor Susan R. Davis is a renowned endocrinologist with a focus on women's health, particularly menopause. She has conducted extensive research on the effects of hormones on women's health, including the impact of menopause on sleep and mood. Professor Davis has received numerous accolades for her contributions to medical research and women's health.
Martha Hickey (MBChB, MD, FRANZCOG)	Obstetrics and Gynecology; Reproductive Endocrinology/ Infertility	Professor, University of Melbourne	Victoria, Australia	Professor Martha Hickey specializes in menopause and menstrual disorders. Her research includes the study of menopausal symptoms such as insomnia and their management. She has contributed significantly to clinical guidelines and has been acknowledged for her work in women's health.
Bronwyn G A Stuckey (MBBS, FRACP)	Endocrinology, Diabetes and Metabolism	Clinical Professor, University of Western Australia	Western Australia	Clinical Professor Bronwyn Stuckey is an endocrinologist with expertise in reproductive endocrinology and menopause. Her research includes the study of hormonal changes during menopause and their effects on sleep and overall health. She has been recognized for her clinical and research contributions to endocrinology.
Jayashri Kulkarni (MBBS, MPM, PhD, FRANZCP, FAHMS)	Psychiatry	Professor, Monash Alfred Psychiatry Research Centre	Victoria, Australia	Professor Jayashri Kulkarni is a psychiatrist specializing in women's mental health, focusing on hormonal influences on mood and cognition during menopause. She has pioneered research into the use of estrogen in treating menopausal depression and insomnia. Professor Kulkarni has received multiple awards for her contributions to psychiatry and women's health.

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